UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,794	07/09/2003	Philippe Horcllou	9430.0003-02	5150

22852 7590 05/26/2005

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/614,794	HORELLOU ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/716,326.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20040806.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

The instant application claims priority to application 08/904,872 and 08/716,326. The specific reference to these applications in the first sentence of the specification (see preliminary amendment made under item 9 of the application transmittal letter filed 7/9/03) should be amended to reflect the change in status of these applications. The '872 application is now abandoned, and the '326 application has issued as US Pat. No. 6,245,330.

Appropriate correction is required.

Information Disclosure Statement

The information disclosure statement filed 8/6/04 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, or of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein as Danos et al. and Peschanski et al., which are not in English, has not been considered.

FR 2688514 and WO 94/20146 are not in English and have been considered only to the extent of their figures and the English abstract in the latter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a replication-defective adenovirus comprising a recombinant adenoviral genome having a non-functional E1 region and comprising all other adenoviral sequences required for replication of the adenovirus in 293 cells and a DNA sequence encoding GDNF, does not reasonably provide enablement for a replication-defective adenovirus whose genome additionally lacks any other region required for replication of the adenovirus in 293 cells, e.g. E2, E4 or L1-L4 genes or encodes an active part of GDNF or a derivative thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claim 1 broadly embraces a replication defective adenovirus. In this context, "replication" means replication of the genome *and* of the adenovirus, i.e. adenoviral virions. The specification discloses and exemplifies an adenovirus made replication defective by deletion of the E1 region. The specification (page 8, lines 6 to page 9, line 4) merely mentions adenoviruses lacking additional regions, such as E2, E4, and L1-L5, as being preferred embodiments, which were the subject of cancelled claim 14. The specification (page 9, line 22 to page 10, line 15) discloses that in order to make replication defective adenoviruses, a cell line that complements the defects in the adenoviral genome is required. The only such cell line disclosed is HEK 293 cells, which contain the E1 region of human adenovirus type 5 and were only known to complement defects in the E1 region, both the E1A and E1B genes, of human adenovirus types 2 and 5. This cell line cannot complement any defects in any other region of adenovirus that are

required for replication of an adenovirus, or adenoviruses where an E1 deficiency cannot be complemented by the Ad5 E1 region.

There is no evidence of record that any other cell line capable of complementing defects in any other region, e.g. E2, E4, and L1-L5, were known or available at the time the invention was made. Kovesdi et al. (US 5,994,106) is directed to making some of these types of multiply replication-deficient adenoviruses. The application for this patent was both filed (11/26/94) and issued (11/30/99) well after the instant invention was made (3/25/94). Kovesdi et al. discloses (col. 4, line 57 to col. 5, line 4) that neither the multiply replication-deficient adenoviruses nor cell lines necessary for producing them were available in the prior art.

Claim 1 broadly embraces embodiments wherein the DNA sequence encodes "an active part" of GDNF or "a derivative" of GDNF. The specification teaches that the vector is for expression of active GDNF *in vivo* in order to treat neurodegenerative diseases by promoting survival of neurons, and at the time the invention was made adenoviral vectors had also been used for producing desired proteins *in vitro*. The specification does not describe what regions of GDNF are needed to promote survival of neurons. Nor does the specification describe any "derivative" that would do the same.

A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the germ of an idea does not constitute an enabling disclosure. While every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the skilled artisan to understand and carry out the invention. It is true that a specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a

rule of supplementation, not a substitute for a basic enabling disclosure. The rule that a specification need not disclose that which is well known in the art simply means that omission of minor details does not cause a specification to fail the enablement requirement, and is not a substitute for an enabling disclosure. However, if there is no disclosure of starting materials and of conditions under which the process can be carried out, undue experimentation is required. Failure to provide such teachings cannot be rectified by asserting that the disclosure of the missing necessary information was well known in the prior art. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 101, 1005 (CA FC, 1997).

The specification does not remedy this deficiency in the prior art, as it provides no guidance or direction for making either the necessary cell lines or the adenoviruses as broadly claimed; nor does it provide any working examples of adenoviruses lacking any essential region other than E1 or encoding other than all of GDNF. Kovesdi et al. summarizes the technical hurdles that had to be overcome to produce replication-defective adenoviruses lacking regions required for replication in addition to E1 (col. 7, line 58 to col. 8, line 12). First, the different gene products must be expressed at appropriate levels and at appropriate times. Second, to avoid cytotoxicity of the gene products of the E2 and E4 regions, it was necessary to employ inducible promoters. The specification provides no indication that these problems existed nor what solutions would overcome them. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific

> laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The instant claims clearly do not bear a reasonable correlation to the enablement provided in the specification, simply because there is none with respect to adenoviruses whose genomes lack replication functions in addition to the non-functional E1 region or an "active part" or "derivative" of GDNF. As illustrated by the disclosure of Kovesdi et al., adenoviral vectors lacking more essential adenoviral genes than E1 could not be made without difficulty and the instant subject matter, like most physiological processes, is unpredictable.

Consequently, it clearly would have required undue experimentation in order to make the replication deficient adenoviruses as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "active" recited in claim 1 is a relative term that renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "active" could refer to any type of activity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds et al. (Curr. Opin. Biol. 4: 734-738, 1993) in view of Le Gal La Salle et al. (Science 259: 988-990, 1993) as evidenced by Strattford-Pericaudet et al. (J. Clin. Invest. 90:626-630, 1992).

Reynolds discloses that several studies have suggested that GDNF may be useful to treat injury or diseases of the nervous system (p. 734, Abstract). Reynolds discloses that GDNF had been purified from rat cultures and used as a probe for the human and rat genes; recombinant GDNF was subsequently made; and GDNF was proposed as a potential treatment for Parkinson's disease (p. 735, ¶1). Reynolds discusses that the hurdle for this therapy lies in the administration of the gene into the CNS and also the size of the gene (p. 734, ¶2, and page 735, last ¶). Reynolds proposes solutions for the delivery problem, including a replication-defective

adenovirus vector. A study done in which a replication-defective adenovirus containing a lacZ reporter gene under control of a viral promoter was specifically cited (p. 736, col. 2, under "Adenovirus vectors"). Reynolds did not actually construct the adenovirus, nor administer it to a subject.

Le Gal La Salle discloses a replication-deficient adenoviral vector containing a reporter gene encoding β-galactosidase (lacZ) that infected rat nerve cells *in vitro* and *in vivo* (abstract). The reporter gene was under control of the RSV LTR promoter (p. 988, ¶2). Le Gal La Salle does not specifically describe the construction of the virus, but cites Strattford-Pericaudet for the construction. Strattford-Pericaudet discloses the construct was made from Ad5 that had been rendered replication incompetent by deletion of the E1 region. Other processing signals for the virus remain intact. It appears that only the E1 region was deleted by replacement with the foreign gene. Le Gal La Salle states "in the context of degenerative diseases, it may be possible to express neurotransmitters or growth factors locally as an alternative to grafting of fetal cells" (p. 990, last ¶). Le Gal La Salle does not incorporate a GDNF gene into their vector not do they specifically suggest it. However, its statement relating to neurotransmitters or growth factors provides motivation to those of ordinary skill in the art to use a gene that is known in the art for such treatment in the vector disclosed, e.g. as in Reynolds.

Therefor it would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art to put a GDNF gene, as disclosed by Reynolds et al., in the adenoviral vector of Le Gal La Salle.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,245,330. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented method uses an adenovirus embraced by instant claim 1.

Conclusion

This is a continuation of applicant's earlier Application No. 08/904,872. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1632